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HARVEY CUSHING'S EARLY TRAINING*

1887-1900

JOHN F. FULTON

You have asked me to speak of Harvey Cushing. After some consideration I have decided that it would be unwise to attempt to touch on all phases of his career and that it would perhaps be more interesting to you to hear something of his early years since they are little known.

The tenth child of a busy Cleveland physician, Harvey Cushing was born on 8 April 1869. His great-grandfather, David Cushing, was a country doctor who lived in the now vanished town of Stafford Hill (Massachusetts) in the Berkshires. David's son, Erastus, records that David was a collector of books and a number of the volumes in his library have come down by direct descent to Harvey Cushing's collection. Erastus, also a physician, finding that the population of Stafford Hill and South Adams (to which he later moved) was dwindling, migrated with his small family to the Western Reserve of Connecticut—that tract of land which became, except for that part lying under Lake Erie, the state of Ohio. He arrived in the village of Cleveland in October 1835 and set himself up in practice. His son, Henry Kirke, the father of Harvey, then only ten years old, was in due time sent to Union College

* Lecture to the Historical Section of The New York Academy of Medicine, 20 March 1946.

and later to Philadelphia to complete his medical studies. Shortly after his return to Cleveland to practise with his father, he married Betsey Maria Williams, the daughter of another pioneering family who had moved to the Western Reserve from East Windsor, Connecticut.

Of the ten children of Henry Kirke and Betsey Maria, seven reached maturity. The eldest, William, was a lawyer; Edward, who was seven years Harvey's senior, became a well-known pediatrician in Cleveland; a third brother, Henry, occupied the Chair of Geology at Western Reserve University; and all had unusual intellectual interests. All, or nearly all, were addicted to collecting—it little mattered what: stamps, coins, leaves, butterflies, etc. Harvey recalls that in his younger days their house in Cleveland was cluttered with albums filled with insects and botanical specimens of every description.

Evidently certain traits of Harvey's character became manifest at an early age, for when less than six the following jingle was perpetrated upon him at a family party:

"Pepper Pot, Pepper Pot, when you were young
They tell me you had a most fiery tongue."

After attending a small private grade school, Cushing entered Central High School in February, 1883, at the age of thirteen years and ten months, and was graduated on Friday evening, 24 June 1887. Dr. J. J. Thomas, one of his classmates, recalls that Harvey, on entering school, was "a short, chubby little fellow, wearing short pants and a little bob-tailed coat, very fashionable at that time for young boys." He and Thomas took the classical course at "Central," and Cushing stood eleventh in a class of eighty-three students, with a final average for the four years of 89.19. In examining grades in individual courses, it is interesting that Cushing stood very high in Latin, which he had studied throughout his four years (average 92); rather less well in Greek, which he had studied for the last three years; and was poorest in English history, in which he scored the grade of 75 during his first year. He was president of the class during his senior year, and at the class entertainment on 16 December 1886 he was on the program as giving a tumbling exhibition with a classmate, as well as taking the part of "Mr. Highflown" in the class play.

During his high school years he had the good fortune to come under the influence of an outstanding teacher, Newton M. Anderson. Mr. Anderson, after graduating from the University of Ohio, was employed

in 1879 by the Bell Telephone Company to install the first telephone exchange at Liége, Belgium. Returning to the United States in 1881, he became an instructor in physics first at the University of Ohio and then at Central High School in Cleveland. Here he began to agitate almost immediately for a course in manual training. Harvey had taken physics under him in 1883-1884 and had assisted him in the apparatus room where he had received some instruction in the use of tools. The following summer (1884) Anderson took Harvey and three of his cousins up the lakes on a fishing expedition, spending most of the summer at a small farmhouse near Sault Ste. Marie. On alternate mornings Anderson took two of the boys down the river to fish, making them row back against the current. The following winter (February 1885) he bought an island of some twenty-five acres, situated in Lake Huron near the Sault River, to which he took the boys during the summer of 1884, along with a number of others from Cleveland, some fourteen in all. To this camp Cushing returned in the summers of 1886 and 1887, and his first letters that have been preserved date from these camping expeditions. In an appreciation of his cousin, Perry Harvey (later his roommate at Yale), Cushing gives a vivid description of the camp:

> To this island we gave the name Maskenoza—the Indian word, I believe, for a pike, which it somewhat resembled in outline—and there we passed most of the following summer [1885], felling spruce with which to build our camp, cooking our own meals, supplying with gun and rod most of our provender, exploring the neighboring country so full of border history, and in leisure time surveying and mapping our small domain.
>
> That winter a staunch 42-foot schooner was built in which, on the eagerly awaited close of school, eight of us sailed from Cleveland to our beloved island, another eight having preceded by steamer to get the camp rebuilt and in running order before the arrival of the schooner with its crew.

In a letter to his mother from Maskenoza (12 August 1887) he writes: "I wish I had brought up a butterfly net this year, for there are more on the island than I have seen before. There is a chrysalis formed on the rafters right over my bed and yesterday Jack brought in a big hawk moth caterpillar, but we could not find out anything for him to eat. So today I let him go as he was getting very meagre. One of the boys brought in the funniest shaped skull I ever saw, which is not

saying much, but we could not imagine what it was so I have preserved it to show to father."

Anderson was convinced that the development of manual dexterity played an important part in the intellectual training of boys, and all of Harvey Cushing's contemporaries in Cleveland have insisted that this early training contributed notably to the shaping of his subsequent career as a surgeon. In referring to Anderson, Mr. Allyn F. Harvey writes: "For myself I can say that he drilled us very thoroughly in the handling of small boats, propelled by oar or paddle, up to thorough ability to handle a 46-foot schooner yacht; he taught us a lot about being independent and made us so by the duties he inflicted upon us during these summer vacations. We were all undoubtedly better disciplined and better prepared for life from the teachings of this man, and from association such as we had with him." And Cushing recalled: "We embryo carpenters progressed to a course of wood-turning with lathes and a year later to metal work at a forge—like so many blacksmiths learning to strike when the iron was hot, the best possible cure for youthful indecision."

Cushing's mother had a kindly nature and she understood Harvey's impetuous ways, but his father was a Puritan much worried about the flesh and the devil, and when Harvey entered Yale he made him agree not to smoke, drink, or consort with those of easy virtue, and above all things, he must not indulge in intercollegiate sports. Harvey, an outgoing Middle Westerner, found himself drawn into the swing of undergraduate activities at Yale within a few days of his arrival in New Haven, and he soon had distinguished himself at the gymnasium in feats of tumbling and had exhibited exceptional prowess on the parallel bars. He was also fond of turning backward somersaults off a six-foot ledge beside the front door of the gym with a lighted cigarette in his mouth. Before he knew it, he had been selected to play shortstop on the freshman ball team, and his batting record proved so unusual that he was promptly put on the varsity nine the following year.

He had kept his indulgence in sports somewhat in the background in his letters home during the first year, and when eventually his father discovered that he was moving around the country with the varsity team and that he was scheduled to go, of all places, to Cambridge, Massachusetts, the floodgates of paternal wrath were loosened, and Harvey found himself in the awkward position of possibly being cut

off from his only source of funds. Henry Kirke Cushing never believed in giving Harvey enough at one time to carry him a whole month—this might lead him into temptations other than intercollegiate sports. Harvey, accordingly, was obliged to send a meticulous expense account every week or two and his funds were never replenished until his last cent had been spent and accounted for.

One of the arguments he offered his father in favor of his playing baseball was the great social advantage of being permitted to sit on the Yale Fence, an honor accorded only to those who had played on a winning Yale team, particularly one which had vanquished Harvard. Henry Kirke did not appear to be particularly impressed by Harvey's ingenuous argument, but he finally sent him his allowance with further stern warnings about scholarship and good behavior. His mother meanwhile had slipped him ten dollars on the side.

His parents possibly had some awareness of their son's unusual talents, for each one preserved separately, and probably unbeknownst to the other, every letter that Harvey wrote from Yale, from the Harvard Medical School, and finally from Johns Hopkins—and he generally wrote to each of them every Sunday, except when there was a crisis such as being "broke," in which case he wrote or telegraphed in the middle of the week. These letters, more than a thousand in number, have all been deciphered and transcribed, and since they give details of his course work both at Yale and at the Harvard Medical School it has been possible to reconstruct educational practices in those days. From these letters also one can trace, week by week, Cushing's rather slow emotional and intellectual development. At Yale he was essentially undistinguished as a student, for he devoted the greater part of his time to extracurricular activity. He became a member of one of Yale's secret senior societies, which he took with the utmost seriousness. "I don't know whether you or any one, except a Yale graduate," he wrote his father, "knows what it is to get an election to Skull and Bones or Scroll and Key. It is the one, the greatest, honor a man can receive in college and is the one thing more than any other sought after by everyone from the time of entering college to senior year and unless I can get an election through athletics I am afraid I will be left out." Later he wrote again: "I won't attempt to tell you what fine things the Senior Societies are acknowledged to be, what a position they hold in the College World and what good they do a man, for if you don't already

know something about it, it would make too long a story. . . ."

It was not until his senior year that he made up his mind to study medicine. Before that time he had thought of architecture and had considered opening an office in New York with his classmate, Grosvenor Atterbury. But Russell Chittenden, who had recently established a laboratory of physiological chemistry at Yale, aroused Cushing's interest in physiology and bio-chemistry during his senior year—an interest easily traced in his notebook of Chittenden's lectures, which contains, incidentally, some unusual sketches of lucine and cholesterin crystals.

It is not clear when Cushing became aware of his artistic talent—but he had had drawing lessons while still in Cleveland. At all events, during his senior year at Yale we find admirable, freehand diagrams exhibiting unusual artistic capacity. During his years at Harvard he sketched continuously. His histology notebook is of itself a work of art, but in addition to laborious drawings over which he no doubt spent much time and energy, he could also catch a likeness with lightning speed, and he was able to convey the whole gamut of human emotions and sensations with a few strokes of his pen or pencil. At clinics he almost invariably drew sketches of the more interesting patients—this to fix them in his memory, both as individuals and as cases exhibiting particular physical signs.

During his medical student years he frequently went off on trips with his family, particularly his brother Edward, and the diaries of such journeys were invariably illustrated with innumerable drawings, many in a light vein, others depicting interesting landmarks and panoramas.

Cushing left Yale in the summer of 1891 and after a vacation in Cleveland he settled on West Cedar Street in Boston, entering the freshman class of the Harvard Medical School, then situated on the corner of Boylston and Exeter Streets. Before he had opportunity to investigate Bostonian dens of iniquity he received another of his father's timeless letters of advice:

> . . . The taking up of new threads in a great new city is a trying, and discouraging process. You can imagine what it is like to one who must do it without help from letters and friends. . . . You will undoubtedly find every day now making you more at home in your new work. And as it is likely to be the front entrance into the work of life, deliberation, constancy, zeal and painstaking endeavor should

mark each day.

Be careful with whom you make acquaintance. It is not every bright and agreeable man that it is safe to tie to. Men go astray in great numbers (even at your age and older) under the temptations of one kind and another that insidiously beguile. No one, I suppose, deliberately goes to the bad, but one step leads to another until deep water is unexpectedly attained.

Playing cards for money, tippling, and the frequenting of haunts of immoral women are the three chief ways in which young men have wrecked themselves in my observation. So far as my observation goes, I have come of late to the conclusion that there is a growing laxity of morals in these regards in the present day. . . .

At Harvard, Cushing worked as hard as he had played at Yale, and almost immediately he became a marked man in his class. One of his contemporaries, Charles Russell Lowell Putnam recalls:

. . . From the day his class was turned into the dissecting room, Cushing became as *eminent* among his fellows as he continued to be among his colleagues throughout life. His first "part" was a right upper extremity, and before a day was passed all the students as well as the teachers were watching the progress of Cushing's dissection. Dr. Mixter had placed him near a window, which in the old gaslighted room was important, and groups of two's and three's often came for a few minutes at a time to watch. Cushing himself talked little. First he sharpened his scalpel carefully and frequently, then he raised his skin flaps so as to keep as many of the cutaneous endings of the nerves as possible intact. At the end of three weeks, he had not only his intercosto-humeral intact, but a multitude of anastomoses from the clavicle to the finger tips. He took the same care of the tissues to avoid drying as he afterwards took in his cranial operations. I should say that he showed his professional preëminence from the start. After the early weeks, he began to talk freely to his fellow workers—but first he stated his intentions. "I have decided to be a leper," he said, and with that phrase he refused practically all social invitations that would have wasted his evenings. . . .

Cushing also quickly distinguished himself during his clinical years, but in January 1893, in the midst of his second year, he had an accident that almost caused him to withdraw from the study of medicine. Substituting for Frank Lynam he gave an anesthetic to a patient with a

strangulated hernia being operated on by Dr. C. B. Porter, and the patient died before the class. He was greatly upset and decided to withdraw from the school, but Porter dissuaded him. Thereupon he and Amory Codman, likewise dissatisfied with the procedure for giving anesthetics, between them worked out a system of continuous recording which enabled both the anesthetist and the surgeon to tell at a glance the condition of his patient, as indicated by pulse and respiration. There was no method available at that time for estimating blood pressure, so that when Cushing several years later saw the Riva-Rocci pneumatic device for recording human blood pressure at Pavia in Italy, he seized upon it and brought it back to the United States. Thereafter his ether charts, as the anesthetic records of Codman and Cushing had come to be called, included a continuous blood-pressure record in addition to pulse and respiration.

On the 8th of November 1945 the fiftieth anniversary of Röntgen's discovery of the X-ray was celebrated in various parts of the world. In the six weeks that followed his first observation Röntgen worked feverishly and established beyond all peradventure of doubt that a Crookes' tube, when activated by a static machine, emitted rays that readily penetrated the fleshy parts of the body without passing so readily through the bone. His announcement of his discovery was made at the end of December 1895 before the Würzburg Academy of Science, and the text of the paper was printed a few days later in its Proceedings. The *Boston Medical and Surgical Journal* received news of the discovery early in February 1896 and in the number for the 13th a detailed account appears, accompanied by an X-ray photograph of the hand. Two days later Cushing, who was then an intern at the M.G.H., wrote enthusiastically to his mother:

> Everyone is much excited over the new photographic discovery. Professor Röntgen may have discovered something with his cathode rays which may revolutionize medical diagnosis. Imagine taking photographs of gall stones in situ—stone in the bladder—foreign bodies anywhere—fractures &c. &c. Mary Crehore sent me two photographs, one of a hand showing in a most mysterious manner the bones of the hand and a ring on the finger which were outlined in a misty way by the normal outlines of the hand. The other of a fracture of the forearm showing the bony displacements. It's fearfully uncanny. We won't be able to have any secrets if people can take

photographs through stone walls &c. Some letters have come from the men abroad telling of the wonderful things they are doing in Vienna with the X-rays."

There is no indication in this letter that a tube was as yet available at the M.G.H. Dr. Codman, writing many years later, states that John Collins Warren brought back a tube in the spring of 1896, but the tube used by Cushing at the M.G.H. appears to be one that he himself had helped to purchase, as is indicated by the following passage in a letter of 10 May to his mother: "We have at last succeeded in having an X-ray machine put in for which I have subscribed largely and hope the conservative staff will ultimately remunerate us for it. It is great sport—very useful in the Out Patient to locate needles, &c. We could look through the chest readily this morning—count the ribs—see the heart beat—the edge of the liver, etc. I will send you some photographs." From this one must infer that a tube or tubes had been in use at the Hospital for some weeks. Dr. Codman, writing in May 1940, mentions that Dr. Warren had probably obtained his tube not from Röntgen, but in England where the focus tube was actually developed.

Dr. Walter Cannon's celebrated work on movements of the gastro-intestinal tract, carried out when a first-year medical student, had commenced in December 1896 and was unrelated to Cushing's earlier clinical studies with the X-ray, for by that time Dr. Cushing had already gone to Johns Hopkins where he had begun a period of service as Halsted's Assistant Resident in Surgery. Cushing took his X-ray tube with him and inaugurated X-ray studies at the Johns Hopkins Hospital. His first clinical report is based on his X-ray studies and it is of some significance in his career, since it dealt with the localization of two neurosurgical lesions—bullets, as it happened, lodged in the vertebral canal beside the spinal cord. These early plates, showing the position of the missile, are surprisingly clear when one considers the primitive tube which Cushing was obliged to use and the fact that the tube was activated by grinding an ancient static machine for some twenty minutes—an interval somewhat too long for a patient to hold his breath!

For four years on Halsted's service Cushing worked incessantly and he found time to make a series of some twenty clinical reports, beginning with his paper on gunshot wounds describing two patients, both of whom had sustained Brown-Séquard lesions of the spinal cord similar to that sustained by General Patton. This was followed by

reports on the surgery of typhoid perforation, local anesthesia with cocaine, a splenectomy for primary splenic anemia, and an important paper describing a method of extirpating the Gasserian ganglion.

The experience at Hopkins proved a particularly valuable one to Cushing, for on account of Dr. Halsted's indifferent health much of the responsibility of his surgical service, both in connection with operating and teaching, fell upon the shoulders of his Resident. It must not be forgotten that Halsted and Osler were responsible for inaugurating the assistant resident-resident system in American medical education. Before that time a promising young surgeon, after a year's internship, during which he might or might not have had opportunity to carry out a surgical procedure himself, was taken on as a junior attending surgeon who then proceeded to gain experience in surgery at the expense of the public. The resident system tended to change all this, for it spread little by little throughout the country. Cushing and Christian were chiefly responsible for starting it in Boston, when the Brigham Hospital was established, and from then on it passed, sometimes from Baltimore, but more often from the Brigham and other Boston hospitals which had fallen into line, to other medical schools, particularly the large state schools in the Middle West and Far West. It has had the effect of placing medical education in the country at large on a plane far higher than that in any other country in the world, not excepting Great Britain. It would be a mistake, however, to believe that the residency system is the last word in medical education. In the first place it has not been universally adopted. For many years the New York schools have held out against it. Your schools have interns and many have assistant residents, but the more prolonged period of training of the residency, so essential for a complete surgical education, has until recently been largely avoided.

Throughout his life, Cushing took a lively interest in all phases of medical education and he was one of those who, though himself a physiologist with a keen interest in all the preclinical sciences, believed that preclinical studies had come to be overstressed in the average medical student's curriculum and that it was highly important to bring students into touch with clinical problems at the earliest possible moment in their medical career. To this end he instituted, first at Hopkins and later at Harvard, a course of Saturday morning clinical lectures for first-year students. He believed that this gave them a more active mo-

tivation for work in general and for their preclinical studies in particular because they were able, through seeing clinical problems, to appreciate the application of their anatomy, physiology, and pathology. In 1925, when called upon to help dedicate the new Sterling Hall of Medicine at Yale, he rather startled his colleagues by comparing the curriculum which Yale and Harvard were then offering students to a heavy-walled cathedral in which the architects had expended so much on the foundations that they were unable to provide a roof. On another occasion, when feeling frustrated over having failed to introduce some improvements in the medical curriculum, he exclaimed that trying to induce his colleagues to alter the curriculum was a little like trying to move a cemetery.

Cushing's first four years in Baltimore had passed quickly and while he was eager to settle down (he had been in love since 1892) Osler and Welch prevailed upon him to spend a year abroad, rounding out his education in some good European laboratory or clinic. He had made one trip abroad with his brother Edward in 1894, but this had been a brief holiday trip of a few weeks and he had not had opportunity to absorb anything of European life or culture. He accordingly sailed late in June 1900 and spent a busy month in England under Osler's wing seeing libraries, hospitals, and attending a round of social functions centering about the Centennial of the Royal College of Surgeons. Osler saw to it that he was invited to the principal gatherings and through that circumstance he was brought into contact with the most prominent figures in contemporary British medicine. In August he crossed to Paris where he spent another week attending meetings, this time the XIIth International Medical Congress which had been organized with all the elaborate continental flourishes of a pre-war gathering. This gave him an opportunity to see and meet many of the important physicians and surgeons of the European continent. He stayed on in Paris for a month, visiting the French hospitals and polishing his French. In October he went on to Lyons, where he was profoundly impressed by the ophthalmologist, Louis Dor, and his erudite father. From Lyons he went to French Switzerland and passed several weeks with César Roux from whom he learned about Swiss thyroid surgery; he also saw some first-rate surgery of the gastro-intestinal tract.

By November he had reached Berne where he settled down for six months, working in the physiological laboratory of Hugo Kronecker,

and in the general surgical clinic of Theodor Kocher. Kocher had never encountered anyone quite like Cushing and for a month he treated the self-assured young American coldly and procrastinated about suggesting a problem on which to work. Cushing grew more and more impatient and by the end of the month he had decided to leave Berne and try his luck in Heidelberg. He had not yet met Kronecker. On advice from his friends he called on the great physiologist and Kronecker, being a much less austere man than Kocher, received Cushing with great warmth and at once made a place for him in his experimental laboratory. Kronecker apparently reassured Kocher about Cushing—he had met self-confident Americans before—and he informed Kocher that if he would formulate a problem for Cushing, Cushing might conduct his studies in the physiological laboratory. Kocher forthwith asked Cushing to investigate the relation of intracranial pressure to systolic blood pressure. As it turned out, he could not have set a problem more suited to Cushing's taste or resourcefulness. Within a few weeks he had developed a procedure for observing the cerebral vessels directly through a window skillfully placed in the skull and, through a second opening, he was able to alter the level of intracranial pressure by raising a drop bottle slung on a pulley from the ceiling of the laboratory. In 1931 when I visited the physiological laboratory at Berne, Professor Leon Asher, Kronecker's successor, showed me with great pride the pulley on which Cushing had slung his pressure bottle thirty years before. The pulley had apparently made a profound impression in Berne because Cushing had screwed it into the ceiling without consulting the Professor.

These studies were finished late in March, following which Cushing went down to Turin in Italy where he spent a month with the Italian physiologist, Angelo Mosso, repeating on dogs the intracranial pressure experiments which he had carried out in Berne on monkeys and cats. He then made a "grand tour" of the Italian hill towns during which he followed the trail of Andreas Vesalius who became something of a patron saint.

He returned to Berne in June to write up the results of his experiments and once again came up against the entrenched continental custom of the professor writing the pupil's paper. It had happened first when Kronecker had called him into the laboratory one evening for the purpose of writing a preliminary report on his results. With sleeves

rolled up and a large pot of coffee beside him, Kronecker began to dictate the text of the paper in German. Harvey Cushing politely but firmly interrupted him, saying, "If you write the paper, it will not be mine and I would not feel free to sign it." After a two-hour argument, Cushing wrote the paper himself. Kocher likewise expected to write up his findings, and we find H.C. writing home: "Most extra-ordinary experience with K. who wished to go over my Arbeit before his departure for Glasgow. Planned for an all-night session, to my astonishment, and then proceeded to write the article as I went over my findings. This I told him was not my way and we had some pretty serious words, fortunately avoiding rocks. Apparently *Selbstständigkeit* is an unusual quality. I was pretty plain with the Professor and told him he could write the article as his, or if he chose to have me publish it, I would do all the work which he could correct and alter as much as he chose." This he did and although doubtless Kocher and Kronecker were both amazed and chagrined at this manifestation of "American ways," it is possible that they were secretly amused, for they remained on friendly terms with their young student as long as they lived.

After more travel on the Continent, Cushing crossed to England where he spent July in the laboratory of Charles Sherrington, the eminent physiologist, who had attracted wide notice through his work on decerebrate rigidity and the functions of the sensory nerves to muscles. He was also beginning a detailed study of the motor area of monkeys and anthropoids. Cushing arrived at a psychological moment in Sherrington's epic research and had the rare opportunity of operating on the brain of both a gorilla and an orang-utang. Sherrington was grateful not only for this surgical assistance, which Cushing was well qualified to give by virtue of his training with Halsted, Kronecker, Kocher and Mosso, but also for the remarkably clear drawings which he made of the anthropoid brain.

During this brief but fruitful stay in Liverpool, Cushing met Alfred Fröhlich of Vienna, then working in Sherrington's laboratory. This was just prior to the time that Fröhlich was to publish his memorable paper describing the syndrome which still bears his name. Cushing left an amusing account in his diary of an expedition with the Fröhlichs to the Isle of Man, made with a view to studying problems of inheritance in tail-less cats. He returned to Baltimore in August 1901 and settled down at the Johns Hopkins where he was to stay until he went to

Harvard in 1912.

Throughout his life Cushing firmly believed that a good surgeon must first become a good physician. His specialization in the surgery of the brain and the spinal cord was therefore based on thorough, early training in the field of general surgery. When he came to the end of his career he had more than fulfilled the promise and ambition of his youth and we can call him scientist, pathfinder, artist, writer, bibliophile, and above all, "a good doctor."

Discussion: ARTURO CASTIGLIONI

I am glad to be able to say some words to you tonight when we are honoring Harvey Cushing. John Fulton has just written his biography, a book which will have, I am sure, a place in the library, not only of every American surgeon and student and of all the people who knew and loved Cushing, but also among the books of all who are interested in learning the history of the development of the personality of a great surgeon and of a great artist. Dr. Fulton has spoken to you of Cushing as a young man, of the years in which his personality was moulded, and has given a brilliant account of this period. Our Chairman and friend, Dr. Leona Baumgartner, whose work I have appreciated for a long time, wrote some years ago some interesting pages about Harvey Cushing as a book collector, and she would surely be more able than myself to describe to you this part of the activity of Cushing. I have only one right to speak on this subject, that is that I had the privilege of knowing Harvey Cushing and of loving his work. I met him several times in Italy, the country he knew and loved, and I had the privilege of discussing with him many things in which we had a common interest. A book lover and a book collector myself, I hoped to be able at last to have my books, very modestly and inconspicuously in the same library where his treasured books found place, but unfortunately the Nazi invasion of Italy has looted my books, and many precious documents I had collected. However, for many years I have worked in Cushing's library in constant contact with his personality, with his mind, with his vivid and always present guidance. The books which he collected are around me, as living witness of the work he accomplished. When I first came to Yale seven years ago, too late to find him alive, I was sorry to have no longer the opportunity of meeting him and having the privilege of his invaluable advice. But later working in the

rooms which bear his name and in which his treasures are collected, I felt that even so I was working under his auspices. There is a figure in Vesalius' Fabrica in which the meditating skeleton looks at the skull on a marble table which has the inscription "Vivitur ingenio, caetera mortis erunt, One shall live through his genius, all else will die." In the library Cushing's genius is alive. I have had the opportunity during my wandering life to work in almost all of the most famous libraries of the world, in the Marciana in Venice, in the Laurenziana in Florence, in the Vatican Library and in the Libraries of Paris and of Oxford. I have had the privilege of seeing and studying the most precious books which present the documentation of the history of human civilization. But Cushing's library is quite different from all the others. The great libraries have generally lost the mark of the personality of the people who bought and owned the books; they are collections of books just as a museum is a collection of works of art, exhibited for the admiration and for the study of the visitor and the name of the donor is listed by a label or an inscription. But Cushing's library is the library of a passionate bibliophile. He had not finished his task at the moment in which the book finally was in his hands. He began to study it, to be interested in the history of the author and of his life, of the people among whom he had lived, of his friends and his publishers, he tried to learn still more about the story of the book itself and of the previous owners, and he was so interested in the book and the content of it that he read it and studied it with the clear eyes of the researcher, with the acute criticism of the diagnostician who is searching for all details, for the places in which the author most clearly and exactly expresses his opinion, but at the same time for the peculiarity of an edition, for the misprints, for the errors in the numeration of pages or the indices. Maybe other people were able to do the same and did it. But we don't know anything about it, and we have not any proof of this peculiar form of passionate love for a book. Cushing was not only a man of genius, but also a practical worker, extremely diligent and exact. He was the type of a man of the Renaissance, the universal man, the researcher, the explorer and at the same time the lover of beauty; the perfect technician who cared for the exact details of the most minute part of his work. But also he was the great artist whose free mind and independent judgment was never definitely bound by any authority. He was, as a great artist of the Renaissance, convinced that there do not exist things of

little importance which may be neglected. The study of the book, of the bibliography, of the typographical characters, of the pages, of the binding had to be exact and correct, no less than the clever examination of the importance of the text. When you look at his drawings in which he was able to catch the character of a person or of a landscape with a few strokes, you understand his personality, just as when you attended any of his operations; he was always careful for the perfection of his technique and for the complete accomplishment of his program. Such were the great scientists and artists of the Renaissance like Benvenuto Cellini who gave to the smallest object which came from his workshop no less attention than he gave to Perseus.

In many books of Cushing's library you find some notes, often pages, written by himself in his fine writing or dictated to his secretary. These pages are a precious mine of information; they are, I believe, the personal introduction of the reader to the author by Harvey Cushing. There you find a discussion on the life of the author and on his activity, some important notice about the publisher and the printer and the time in which the book appeared; then information about the success of the book, the price it was sold for, the judgment of critics and of readers; finally, a series of small observations on differences between this one copy of the book and other copies in other libraries, on the rarity of the book; on the price for which Cushing had purchased it, from whom, where and under what conditions. In other pages you find a summary of the contents and a quotation of the most important passages. We can say that after reading Cushing's introduction, the book or the manuscript of the ancient author is no longer unknown to you, his work is not distant and inaccessible; on the contrary you have the feeling that somebody who is an expert has taken you by the hand showing you the way. You are encouraged and you proceed with the belief that you will be able to find surely and easily what you like.

Cushing's choice of books speaks eloquently for his education, for his taste, and for the universality of his interest. He collected medical books and was chiefly interested in Vesalius and the books on anatomy in the Renaissance, but besides that almost any chapter of medical history had an appeal to him; all books on magic, on astrology, on philosophy, and in general on every current of ideas directly or indirectly connected with medicine awakened his interest and his curiosity. One of the most precious books of the Cushing library is the famous Calendar by Johan-

nes Regiomontanus printed in Nuremberg by the private press of the author in 1474. It is one of the most beautiful, probably the most perfect copy extant of this book, surely better than the copy of the British Museum. It is the extremely rare *editio princeps* of the celebrated Calendar which was the prototype of all calendars in book form, and contains the astronomical tables and tables for calculating dates and festivals for 1475-1513. There are more than fifty wood cuts, illustrating eclipses of the moon and sun, and a chapter on the best time for bloodletting. In the book you find a notice of ten pages of information inserted by Cushing with the exact description of the book, with the story of its author, with the life of the man who owned the book, a certain Serlinger, Bishop of Sekkau, near Strassburg, and eventually the description of the tombstone of this Bishop. When you have read his learned introduction you are able to appreciate the importance of the book and the rôle that books of this type which are now extremely rare have played in the history of the culture of the middle ages.

On many occasions Cushing admitted the firm hold books had on him and he described book collecting as "Worse than the opium habit, but much more fun." He wrote also about it in his "Apologia" which is an introduction to the bio-bibliography of Vesalius: "The slowly progressive so rarely fatal malady, bibliomania, while commonly a masculine ailment, easily leads to difficulties because of an even more serious counter-disorder which is prone to affect the distaff members of the family, who usually control the majority vote. They show an uncontrollable tendency to accumulate odds and ends which mysteriously find their way, under the general name of antiques, into the house late in the day by way of the garage after all identification tags have been removed. On the other hand a new old-book unmistakable in its brown paper parcel and bearing unfamiliar foreign stamps is handed in openly at the front door by the postman, thereby advertising its arrival from parlor to kitchen. . . . Most collectors of books in self defense conceal them in their so-called dens, fully convinced that they have made a better investment for the long pull than has the party of the first part."

Speaking once at the dedication of the medical library in Cleveland he said: "I warn young people against book-collecting for one may easily become enslaved and soon so enveloped by books that they are on the floor and out in the front hall and in the dining room till you never can find the volume you want and feel sure your wife or the

children must have taken it from the place you last put it, when they borrowed your paste pot and scissors. . . . In fact beware of books; as a species they are imperishable and against their multiplication nature has no chance whatsoever. The time will come when every tree has been felled for paper, every calf for leather and the few-longhaired and undernourished people left in the world will be madly making card indices of the volumes which have filled every available cranny in which they can be stored. Yes, beware of books as an expensive habit and waster of time."

A very nice story characterizing the passionate book-collector was told by Cushing in the same oration. "A friend has been staying with me whose metabolism and pulse rate in the presence of other people's books run high. He grows exophthalmic with hyper-biblioism so while you endeavor to concentrate upon your task he exclaims: 'Where did you get this Dolet imprint?' holding up a vaguely remembered calf of a book in his hand. 'Oh I don't remember, someone may have left it at the door, but I always thought it came into being on the bottom shelf of that case in the corner.' 'Are you aware,' says he, ignoring my trivialities, 'that Christie knew of only one other copy?' You begin to take interest. 'Perhaps someone gave it to me for Christmas. But what about Dolet? Let me see the book; it's only just grown up.'

"And there it was, sure enough—*A Lyon. Chés Estienne Dolet, 1542. Auec priuileige pour dix ans.* And, what is more, with two other Dolet imprints, *Des Tumeurs* and Galen's *De la Raison de curer par Evacuation de Sang*, newly translated from the Latin into French by the printer—a veritable triplet.

"This is enough; you are lost. The attack is on. Influenza in its abruptness is nothing to it, and days elapse before you are fit to resume your legitimate job. Your fever leads you first to Richard Copley Christie's life of the unfortunate Etienne Dolet, the young Renaissance scholar and printer, . . . and then you are anxious to know about Christie. . . . Beware the book."

Harvey Cushing did not follow this humorous advice he gave to his audience; he loved the books; he followed the traces of the books, authors, their publisher and their printer. He liked to state, as far as possible, the influence which a book had on the current of thought of its time, the people who copied and plagiarized it, the enemies who attacked its author, the friends who defended him. He became a clever

historian of medicine who, starting from the details arrived at the main problems of medical history, just as an explorer who, taking his way from a hidden and unknown place, arrives through roads he never had passed before to the main road of human thought. He was therefore also able, as a book collector and as a great teacher, to inspire other people through his example and through his suggestion with a love for books and interest in historical studies.

Harvey Cushing is one of the many examples that we know of a scientist and an experimental researcher, of a surgeon and physiologist who never lost his fundamental character as a humanist. He was a humanist in the most noble sense of the word. He possessed the feeling of the cultural tradition of humanity intended as continuity in thinking and in learning humanism as a cult of beauty and a search for glory. Like Leonardo who was the great man of the Renaissance, no less a great scientist than a great poet, anatomist, mathematician and mechanician, Harvey Cushing was a complete personality and his work as book collector is only one interesting facet of his individuality. In this field all the outstanding qualities of his temperament and of his genius are expressed no less than in his work as physiologist and as surgeon. In this field as in all fields of his work the saying written on the marble on which Vesalius' skeleton is meditating is true; *Vivitur ingenio;* through his genius one may survive.

THE CAUSES OF CANCER

*The Annual James Ewing Memorial Lecture**

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I WISH to thank Dr. L'Esperance and the other members of the Committee for their invitation to deliver the Memorial Lecture in honor of Dr. James Ewing. Memories of many years past lead me back to my acquaintance with Dr. Ewing. Between the years from 1903 to 1910 when I was associated with the University of Pennsylvania, I had occasion to visit New York and to meet Dr. Ewing at various times. We were both interested in Cancer Research. Dr. Ewing at that time carried out among other studies investigations into the nature of the so-called infectious tumors of dogs. He was thus one of the early investigators in the field of Experimental Cancer Research; but from the beginning he was also greatly interested in the Pathology of human tumors and he produced later his authoritative book on "Neoplastic Diseases" in which he analyzed with a keen scientific spirit the principal data which are of importance to the pathologist and especially also to the physician. He has thus exerted a great influence on medical science, theoretical as well as applied, not only in this country but also in other countries wherever his work became known. He contributed original investigations especially concerning the nature of bone tumors, where one type bears his name. He combined thus in an outstanding manner an interest in and a profound knowledge of experimental cancer research and of the pathology of human tumors.

I cannot claim for myself the same universality of interest. My studies were concerned largely with the experimental growth of tissues and tumors and I have carried on research in this field for more than fifty years. I shall here endeavor to present a picture of the different directions in which cancer research has extended and of some of the

* Given May 1, 1947 at The New York Academy of Medicine.

trends of cancer research during this period and of what I consider the essential, though tentative conclusions that can be formulated at the present time.

Theory of Cancer

We shall first recall a theory which we stated in 1916 and which we had occasion to restate repeatedly since then. It may be formulated approximately as follows: Cancer develops if a combination of stimulating factors and of genetic factors makes possible a series of growth processes, which gain gradually in intensity. Intermediate steps in this continuous process of cancerization are represented by states of increasing sensitization, as a result of which specific stimuli no longer are needed for the tissue to reach the state of cancerous growth, but in which non-specific or less specific factors can accomplish it.

It has been assumed by some investigators in recent years that at the time when the tissues no longer needed specific stimuli for the completion of the process of cancerization, a transformation of some tissue cells into cancer cells had already occurred and that these cancer cells subsequently gave origin to the cancerous growth. However, there are several considerations which seem to make this interpretation less probable than the assumption that intermediate stages between normal tissue cells and typical cancer cells exist and that such intermediate tissues may react as would sensitized tissues.

The genetic hereditary factors seem to act in the process of cancerization, principally by making the tissues more responsive to growth stimuli. But even after the cancerous state has been reached, the process of stimulation does not necessarily cease; it may continue and intensify the cancerous change and increase the proliferative and invasive action of the cancer cells. Concomitantly with the continued stimulation of the tissue the chemical and morphological constitution of the cells is modified. The tissue thus becomes more and more independent of the action of the external growth stimuli of various kinds. As the result of this long continued activity of the external stimuli in coöperation with the genetic factors, there gradually develops a growth factor within the cell and presumably within the cytoplasm, which incites the cell to continuous growth. The cancerous change affects principally the organ and tissue differentials, which means those cell characteristics which differentiate the different tissues and organs within the same individual,

while they leave the characteristic which is common to all the organs and tissues within the same individual, strain or species, the individuality and species differentials, to a large extent unaltered. The inner growth factor which has been created has the power to propagate autocatalytically. Thus the cancerous condition has become permanent.

Although cancer differs from all other growth processes in very characteristic ways, yet the various factors which are the cause of all the other growth processes, such as hormonal and regenerative or embryonal growth, may also act as causes of cancerous growth, but only as partial causes which need to be supplemented by the action of genetic factors. They represent the stimulating factors, which ultimately lead to the production of the inner growth factors, provided the genetic constitution is favorable for such an effect.

General Characteristics of Growth Stimuli

In a general way we can divide growth stimuli into two classes: 1) Those which exert a direct stimulation of growth without first inflicting an injury on the cells. Growth hormones are an example of such factors, and 2) other factors which primarily cause a tissue injury which is followed by growth processes of a regenerative nature. Both of these classes may be active in the induction of cancer. There are probably conditions of an intermediate nature, in which external factors alter the cell equilibrium in an abnormal way and thus inflict injury, but in which the damage is not so great as to lead to visible pathological changes in the tissues.

Stimulating Factors in the Development of Cancer

As stated, growth factors in general may function as stimulating agents in the formation of cancers. This effect of stimulating factors in the production of cancer does not, however, mean that all of these factors are equally effective in producing cancer or that in addition some special growth factors which do not play a role under ordinary conditions may not also be active. Such special factors do exist largely in the form of tar and of certain polycyclic hydrocarbons, but these also, as far as is known, seem essentially to represent growth inductors which do not in principle differ from all the other growth factors mentioned. Yet because they are not known to play a role under non-cancerous conditions, and because they are very effective as cancer

inductors, there has evolved in many investigators the implied or openly expressed conviction that these hydrocarbons are the real, though hidden causes of cancer which are active when cancer arises apparently spontaneously without any known efficient cause. As far as it can be determined these cancer producing hydrocarbons act as direct growth stimulators and do not call forth a primary injury which would then be followed by proliferation. It is very probable that they are so effective as cancerigenic agents, because they are so effective as growth stimulators of tissues. Of special interest in addition to the cancerigenic hydrocarbons are certain azodyes, such as p-dimethylaminoazobenzene, o-aminoazotoluene, and substances such as carbon tetrachloride and chloroform which produce malignant tumors in the liver of rats and mice when fed by mouth or after parenteral administration. In all probability they cause primarily injury of the liver cells either directly or in association with deficient diets and these effects are followed by regenerative and compensatory growth processes which by way of adenoma step by step pass into malignant cholangioma and hepatoma. Whereas ordinarily under-nutrition tends to delay or prevent cancerous growth in the case of these tumors dietary deficiencies of a certain kind by causing tissue injury, may lead to the formation of cancer. These and various other problems have been studied in this country especially by Rhoads, Kensler, Dobriner and Sugiura, Chambers; by Miller, Baumann and Rusch and by Andervont, White, Edwards and Eschenbrenner and by Opie.

Hormones as Stimulating Factors

Before the effectiveness of these two types of substances in the production of cancer had been discovered, it was found in 1915 and the following years that hormones and above all others sex hormones may act as potent agents in the production of spontaneous cancers. They are the only cancerigenic substances known so far which are normal constituents of the animal body and which here exert a normal function mainly and primarily as growth stimulators in the accessory sex organs, and as a result of this function, may cause the development of cancer in the organs in which they normally induce growth processes. They also control here various metabolic activities and secondarily they affect certain other organs. They do not as a rule act locally at the site of injection, except in the organs to which they have a specific affinity;

nor is their chemical constitution as such of importance; the essential condition is that wherever applied, they induce proliferation in specific organs and in these they induce cancerous changes; therein, as well as in some other respects, they differ from the cancerigenic hydrocarbons. But hormones and cancerigenic hydrocarbons and also azodyes resemble one another in that they all act in coöperation with genetic factors. While the cancer producing action of hormones is exemplified so far by the sex hormones and especially by estrogen in its action on mammary gland, vagina and cervix, and also on the interstitial gland of the testicle, as Bonser and Gardner have observed, and on the anterior hypophysis, it could be predicted in the beginning of our investigations that presumably other hormones might exert corresponding effects. More recently it has been observed by Woolley and Little that also adrenal cortical hormones may exert a cancerigenic action and by Bielchowsky that thiourea acting in a hormone-like manner on the thyroid gland may, in coöperation with aminofluorene, induce tumor formation in the thyroid gland.

As far as is known at present in every case of experimental cancer induction under the influence of hormones and of cancerigenic hydrocarbons, a period of sensitization precedes the cancerous end process; moreover cancer is not caused by the action of the hormones on single cells of the recipient organ, but on the structural organ units, and the same fact applies to the action of some other cancerigenic agents. But in contrast to certain other cancer producing factors hormones induce these growth processes and thereby cancer not by means of primary tissue injury, which would be followed by secondary regenerative proliferation, but by a direct stimulating action on the tissue substratum.

Clinical observation has shown the importance of tissue injury as one of the causes of cancer. In experimental cancer, trauma has been established as one of the coöperative causes of cancer in the case of cancer of vagina and cervix and of the epidermis in mice. In both the clinical and the experimental cancers the tissue injury must be long continued or often repeated, it must be chronic, in order to be effective.

X-rays, gamma rays and ultraviolet light may act as cancer inductors in tissues which are able to absorb these radiations. They seem primarily to cause tissue injury, in addition to mutations which they may induce in germ cells. However there exists after all the possibility that these radiations may also be able to induce primary growth by way

of direct tissue stimulation. This is conceivable because there are strong indications that tissues at a certain stage may become actively immunized against these injurious actions, and that thus the injurious actions are mitigated. In this connection the observations of Furth on the production of ovarian granulosa cell tumors in mice by the action of X-rays in certain strains of mice may be of special interest; it may perhaps be possible to determine whether these tumors may not develop without a preceding injurious action of the X-rays on the tissue substratum.

Cancer may be caused by metazoic parasites. It appears most likely that directly or indirectly, as the result of the activity of these parasites, substances are produced which stimulate the surrounding tissue to grow and to become cancerous. Although no definite demonstration of the existence of such substances has been given so far, the recent experiments of Dunning and Curtis suggest that substances or agents present in the parasites may be responsible for the cancerous change.

As to the mode of action of these various stimulating factors, they seem to have in common the characteristic that through successive stimulations they initiate growth processes which occur in certain rhythms and that each stimulation at least tends to be followed by a return of the affected tissue to its original state; the processes induced by the stimuli would then approximately be cyclic. But such a return to the normal condition is not complete and therefore an accumulation of successive growth stimulations will take place and in the end this will lead to the production of cancer. The cancerous transformation resulting from the accumulation of successive growth stimulations would take place by way of an intermediate state of tissue sensitization.

Genetic Factors in the Origin of Cancer

The various stimulating agents which we have discussed so far can produce cancer only if they have a chance to act on a tissue substratum which is able to respond to such stimulations with growth processes of a certain intensity. The mode of response of the tissue is dependent largely on genetic factors, which latter determine the constitution of the reacting tissue. It has been found that on the whole the tendency to cancer formation of different organs differs greatly within the same individual; and that these differences are characteristic of the species

and especially of the individual and of the strain to which the individual belongs, provided the strain has been made relatively pure through close inbreeding. However, a completely pure strain does not exist, as transplantation experiments between individuals which are members of such a strain have shown. It seems that in each individual a slight remnant of its own individuality differential persists through many generations of brother to sister matings. As stated, different organs of the same strain or individual differ greatly in their tendency to develop cancer and this tendency in one organ of an individual seems to be independent of that in another organ of the same individual. These tendencies are therefore determined mainly by the genetic constitution of the various organ and tissue differentials, and they are a part of the mosaic genetic constitution of the individual.

There are valid reasons for assuming that multiple genetic factors are concerned in the origin of cancer and that furthermore in general a quantitative relation seems to exist between the strength of the stimulating factors (S) and of the genetic hereditary factors (H) in the production of cancer (C) which can be approximately expressed by the equation H x S = C. The stronger the genetic factors are, the less strong do the exogenous stimulating factors need to be, and vice versa, in order to accomplish the cancerous transformation. In certain cancers which develop on an embryonic basis, the sensitization of the tissues involved seems to be so great that apparently non-specific factors may induce the development of cancer. According to the recent investigations of L. C. Strong it seems also that in a number of substrains of mouse strains N H and N H O, it is principally the genetic factors which determine the development of cancer in various organs; and different organs seem to exhibit this tendency in different kinds of these substrains, which latter owe their origin to germinal mutations. In the main these tumors behaved in a similar way to those that develop on an embryonic basis. In both conditions it appears as though we had to deal with sensitized tissues which no longer needed specific stimulating factors for the induction of tumors.

Besides these types of cancer which seem to be predominantly inherent in the constitution of the tissues there are others which are caused largely by the action of external conditions and in which genetic factors are of minor importance owing to the great intensity with which such external factors act. For instance, in the case of long con-

tinued application of X-rays to the unprotected human skin, it seems that cancer develops in almost all individuals irrespective of their genetic constitution.

As to the mode of action of the genetic factors, they may in some cases exert their effects indirectly through initiation of other predisposing factors; thus, for instance, certain diseases which develop partly on a genetic basis may promote the subsequent development of cancer; but as a rule genetic factors act by affecting the degree of responsiveness of the organ subjected to specific growth stimulating factors. According to Little and to Heston, Deringer and Andervont in the case of the carcinoma of the mammary gland in mice, also the propagation of the milk factor which may coöperate with hormones in the development of this tumor seems to be controlled by genetic factors; those genetic factors which cause a high degree of responsiveness of the mammary gland to stimulation by hormones also promote the propagation of the milk factor.

It is especially those investigators whose interest has centered mainly in the genetic hereditary factors in cancer and those who have studied the nuclear and chromosomal changes taking place in tumor cells or in tissue cells, during or preceding their transformation into cancer, who, on the whole, have favored the theory of mutations in tissue cells, somatic mutations, as the essential cause of cancer. However, there are several considerations which make this interpretation very improbable and we may conclude that somatic mutations due to changes in genes and chromosomes are in all probability not concerned in the origin of malignant tumors. This conclusion applies only to somatic mutations and not to germinal mutations—mutations in the genes or chromosomes of the germ cells. It is very well conceivable and even probable that germinal mutations are involved in cancer development; that they may determine the degree of responsiveness and sensitization of a certain organ or tissue to growth stimuli of various degrees of specificity and intensity and that in some instances the responsiveness may become so great that the ordinary metabolic and mechanical changes concerned in the process of living are sufficient in the end to induce cancer formation. In this case endogenous genetic, inheritable factors as such may be able to induce development of cancer and specific extraneous stimuli apparently are not needed. For instance there seems no reason for assuming that ovarian hormones produce the usual series of changes in

the mammary gland, cervix and vagina, namely first ordinary growth, then hypertrophy to be followed by adenoma and in the end cancer by means of somatic mutations. However, these objections to the application of the term "somatic mutation" hold good only, if we use this term in the strict genetic sense. If we extend the definition so as to include not only changes in genes and chromosomes but also a series of steadily increasing cytoplasmic changes, then the origin of cancer may be attributed to somatic mutations, and we also have formerly used this term in this wider sense. But before doing so, there should be a clear understanding as to the manner in which this term is defined. The conclusion that somatic mutations in the strict genetic sense in all probability are not the essential cause of cancer carries with it the implication that also cytoplasmic factors, and not solely nuclear factors, may be involved in the development of cancer. In favor of the importance of cytoplasmic factors, there may be cited, besides some older observations concerning the propagation of certain cytoplasmic cell constituents, the recent observations of Sonneborn in Paramaecia aurelia and of the Lindegrens and Spiegelman in Saccharomyces. Both of these sets of observations agree in regard to the importance of cytoplasmic factors in the hereditary transmission of cellular characteristics and also in the origin of these factors from the nucleus. As far as the development of cancer is concerned, these investigations lend support to the view that also in this case cytoplasmic factors may play a significant role.

The Interpretation of These Data

The multiplicity of external causes of cancer which have been observed led some investigators to look for one underlying common factor to which all the others were subordinated. It was especially Borrel, who in the early part of this century upheld the view that this common factor consisted in a virus, which was carried to a tissue with the help of the various other factors mentioned, which latter were thus of a subsidiary nature. On the other hand we expressed the view that the common underlying conditions present in these various stimulations were the long continued and gradually intensified growth processes which were induced in the tissue substratum and we furthermore found evidence for the conclusion that by way of tissue sensitization these growth processes as such, or processes intimately connected with them, led in the end to the cancerous transformation of the normal tissue. As

stated, the increased growth and also motility of the tissues exhibited under these conditions were attributed by us to the production of an intracellular growth substance, which propagated within the cells autocatalytically, and the automatically continued production of this substance was considered responsible for the irreversible character of cancer. We thus distinguished between multiple exogenous growth factors (eg) which coöperated with genetic factors and the autocatalytically propagating inner growth factor which resulted from this cooperation. It was also suggested at that time that under certain conditions such an autocatalytically propagating growth substance might be separable from the tissues; it might then be experimentally transmitted to related hosts and here induce cancerous changes. This growth substance (ig) might thus act like a virus, although it was of endogenous tissue origin. We believe it very probable that the concept of autocatalytically propagating growth substances of endogenous derivation applies to the large majority of tumors in animals, including man. As pointed out by us somewhat later there exists in addition under certain conditions an analogy between the action of cancer producing stimulating factors and the action of organizers or inductors in embryonal development, where through contact action they transform one kind of tissue into another.

When it was found that one type of pneumococci can be transformed into another type under the influence of a substance present in the second type, Murphy compared such mutagenic substances with the action of avian sarcoma agents which transform normal cells into sarcoma cells. A further similarity between the avian sarcoma agents and the substances which change types of pneumococci consists in the fact that according to Avery the transforming substance in pneumococci is a nucleic acid and that viruses also consist of nucleic acid-protein combinations with or without the association with lipids. However whereas the type-changes in pneumococci take place suddenly and rapidly, the cancerous transformation of normal tissue cells into cancerous cells takes place step by step and requires as a rule a long period of time. The usually rapid action of the avian sarcoma agent seems to be an exception to this rule; we have already referred to the possible interpretation of this effect and we shall discuss it again in another connection. These observations lead us to a consideration of

Viruses as Cancer Agents

The essential data in this field we owe to the investigations of Peyton Rous and his associates, especially Beard, Kidd and Friedewald, and subsequently other investigators have made important contributions. In four types of cancer, viruses or agents resembling viruses may play a part in the induction of the cancerous growth: 1) In certain cases of fowl sarcoma it has been found by Peyton Rous and also by Fujinami that in some tumors filterable agents can be separated from the tumor cells. 2) The benign papillomatous tumors discovered by Shope, in cotton tail rabbits, can be induced by a virus and under certain conditions can change into carcinoma. 3) The mammary carcinoma of the mouse in which a virus-like substance, discovered by Bittner and present as a rule in the milk and in some organs of mice, belonging to high mammary tumor rate strains, may play an important role in the carcinomatous transformation of the mammary gland tissue. 4) There are indications that adenocarcinoma of the kidney in Rana pipiens may be caused by a virus (Lucké).

The agents of avian sarcomas are situated in the tumor cells; they are filterable through filters that retain the cells. In very young chickens in which the resistance to the virus is as yet very slight, the latter may give rise to generalized hemorrhagic lesions instead of to tumors (Duran-Reynals). In an adult chicken which bears such a sarcoma antibodies may develop against this tumor. As Rous has found the sarcoma virus tends to fix itself to growing tissue and according to Murphy it is absorbed specifically by muscle of fowl in contradistinction to muscle of other species, and herein as well as in certain other respects it shows fowl-specific characteristics.

Beginning with the experiments of Murphy and Landsteiner attempts have been made by various investigators to determine whether or not in chickens, in which a sarcoma has been produced by injection of tar or carcinogenic hydrocarbons, the presence of a sarcoma virus can be demonstrated. It seems that in a few experiments of McIntosh and Selbie such a virus has been found. However the large majority of such experiments, especially those of Murphy and Peacock, were negative, and it is very probable that as a rule avian sarcomas which are induced by cancerigenic hydrocarbons do not contain a virus.

As to the mode of origin and nature of these tumor-producing vi-

ruses, no definite statement can be made.

1) *The virus of rabbit papilloma.* Shope discovered in the papilloma of the skin of cotton tail rabbits a virus which can be transmitted to the epidermis of the domestic rabbit and here also give rise to papilloma formation. In the latter species the papilloma may in the course of time become transformed into squamous cell carcinoma, in which as a rule the virus can no longer be demonstrated by inoculation experiments. However, antibodies against the Shope virus may form in such rabbits. The relation existing between the papilloma and the carcinoma developing from the former have been studied mainly by Rous and his collaborators, Kidd, Beard, Friedewald and McKenzie. They observed that a papilloma, which developed in domestic rabbits following inoculation of the papilloma virus, can be changed into carcinoma by application of tar, and conversely that a tar papilloma in a rabbit can be rapidly transformed into a carcinoma by intravenous injection of papilloma virus. Both of these agents, tar and virus, seem therefore to act in principle in a similar manner.

2) *The milk agent.* The agent present as a rule in the mammary gland of mice, belonging to high mammary tumor strains, is transmitted with the milk of the mother to the young (Bittner) and then may coöperate with genetic factors and with hormones in the production of mammary carcinoma. But in order to be effective the milk factor has to act on the mammary gland of the mouse at an early age. It seems to fix itself on the mammary gland tissue and it helps to accelerate growth processes which ultimately lead to cancer formation. However, under the influence of carcinogenic hydrocarbons mammary carcinomata may develop without the coöperation of the milk factor. These tumors are essentially like those which develop under the influence of ovarian hormones; differences which exist are merely of a quantitative nature. It seems moreover that also under the influence of ovarian hormones, in particular estrogen, mammary carcinoma can develop without the coöperation of the milk agent. Carcinomas of vagina and cervix, as well as all other types of cancer which are produced by estrogens or other stimulating agents, are not apparently influenced by the milk factor, although in leukemia it may perhaps have a very slight effect, not identical with that exerted in mammary carcinoma (Furth), nor has it so far been shown that the milk factor is active in any species other than the mouse. All these facts do not favor the interpretation

that the milk factor is the real "inciter" of mammary carcinoma in the sense in which the avian carcinoma agent is the cause of fowl sarcoma, and that the ovarian hormones are only of secondary importance. On the contrary all data point to the conclusion that the ovarian hormones represent the essential stimulator of mammary carcinoma as well as of certain other tumors, especially those of the accessory female sex organs and those of the pituitary and of the interstitial gland of the testicle, and that the milk factor acts as a subsidiary growth factor in the production of mammary carcinoma of mice.

The mode of action and significance of viruses in the production of cancer. The findings concerning the production of certain cancers by means of viruses suggested to Rous, Andrewes and others, the theory that viruses may be involved in and be the immediate cause of all types of cancer and that all the other known cancerigenic factors are merely of secondary importance, enabling the viruses to fix themselves on tissue cells and perhaps inducing them to undergo mutations, thus rendering them cancerigenic. Such a concept presupposes that viruses are present, though in an inactive state, in all organs and tissues of organisms liable to become cancerous, including embryonic organs. This conclusion rests on the assumption that cancer-inducing viruses are tissue and organ specific. This seems to be largely true, although to a limited extent such viruses may apparently act on more than one type of tissue. The necessity for assuming the constant presence of distinct viruses in so many different organs and tissues of each individual has suggested more recently to Altenburg the view that viruses may have invaded all the tissues of higher organisms in earlier phylogenetic periods and that since then they continue to inhabit these organs as symbionts (viroids). This hypothesis would then imply the interpretation that endogenous autocatalytic growth substances causing the production of cancer were originally extraneous organisms which as symbionts had become adapted to the host cells.

However, there must be considered at least two distinct modes of action of the cancer-producing viruses which are known so far. The agents of avian sarcoma seem to accomplish the cancerous transformation directly and rapidly through invasion of a specific tissue, especially one undergoing temporary growth processes. As far as the invaded cells are concerned, all they need in order to become cancerous is to accept the virus. Yet, it has been found that, as the result of the invasion by

viruses, these cells have acquired new metabolic characteristics which distinguish cancerous tissues from normal ones. On the other hand, the virus of rabbit papilloma and likewise the milk factor seem to act by inducing growth processes in the normal tissues which are gradually intensified and in coöperation with other factors in the end lead to their entering the carcinomatous state. These viruses behave therefore essentially like the other stimulating factors or they may act by intensifying the response of normal tissues to other stimulating factors. They lead to active metabolic and other changes in the tissues and thus also to proliferative processes which end in the transformation of these cells into cancer. However, as stated, also the fowl sarcoma agent seems to induce active changes in the cells it has invaded, and, moreover, in some instances, it apparently requires a longer time in order to accomplish the cancerous transformation of the mesenchymal cell. The difference in the cancerigenic action of these two types of viruses may therefore after all not be of a radical nature.

When it was found that cancerigenic viruses cannot as a rule be demonstrated in mammalian cancers—and the recent experiments of Woglom confirm this conclusion—the attempt was made to demonstrate their presence by immunological methods. It is probably this aim, based on the conception that a virus is the immediate cause of every type of cancer, that gave rise to the immunological studies of Kidd. In these experiments Kidd analyzed the nature of the antibodies which develop in rabibts implanted with the Brown-Pearce rabbit carcinoma. He found that two types of antibodies develop: 1) one which is specific for the antigen of the Brown-Pearce tumor cells, and 2) one which reacts also with normal rabbit tissues; there exists in addition 3) a natural antibody which is present even in rabbits which have not been implanted with Brown-Pearce tumor and which reacts with the cancer cells as well as with normal rabbit tissue. Also another rabbit carcinoma V2 which had originally developed from a Shope rabbit papilloma was found to possess an antigen which could give rise to the production of a specific antibody and which differed from the antibody directed against the Brown-Pearce tumor. Because these specific antibodies reacted also with Claude's microsome fraction of the tumor cells and furthermore because there was no indication of the presence of a virus in either of these two tumors, Kidd inclines to the conclusion that in both of these cases a cell constituent, rather than a true virus, acted as antigen and

that this antigen may perhaps have functioned in a way similar to the autocatalytic intracellular growth substance which according to the theory discussed already, is supposed to be the immediate direct cause of carcinomatous growth. These experiments of Kidd then support the view that it is not likely that true viruses are responsible for the origin of the large majority of mammalian cancers, although in certain instances there is a probability that such viruses may be involved. Also the recent experiments of Rous and Smith, in which they succeeded in producing cancer in two different embryonic organs, through direct application of methylcholanthrene to transplanted embryonic material, taken together with some supplementary experiments, are unfavorable to the view that viruses must be the cause of such cancers and therefore of mammalian cancers in general. Yet in addition to the conditions already mentioned there are some other conditions in cancer development which might leave open both possibilities, namely, that either true viruses are involved or that autocatalytically propagating growth substances are the essential cause. Conditions of this kind are: 1) The long known fact that in the course of serial transplantation of tumors as a rule an increase in growth energy of the transplanted cells takes place. Is this due to the stimulating effect which the process of transplantation exerts on one of the cell constituents or is it due to a change which takes place, as a result of the transplantation, in a virus previously introduced into the cell from the outside? 2) The observations, likewise dating back a long time, that the growth of carcinomatous epithelium may induce a sarcomatous transformation in the adjoining stroma. Is this due to an organizer like action emanating from the carcinoma cells or to the transfer of a virus from the epithelium to the connective tissue? 3) The experiments of Taylor and his associates in which carcinomatous tissue was cultivated in the yolk of chicken eggs. Injection of cell free filtrates of such yolk into mice seemed to be followed in certain cases by the development of sarcoma. 4) Experiments by Silver in which cell free filtrates from mouse sarcoma in its early stages of development–a tumor induced by 1, 2, 5, 6–dibenzanthracene–after injection into other mice, gave rise to sarcoma formation. Likewise in recent experiments of Herly transfer of ascitic fluid, produced in the peritoneal cavity of mice through the injection of methylcholanthrene, to the peritoneum of other mice could under certain conditions give origin to sarcoma formation. 5) According to A. Fischer repeated auto-

transplantation of normal mammary gland tissue may result in carcinomatous changes in the transplant and Earle observed that after long continued growth of mouse fibroblasts in tissue culture their transplantation back into the mouse led to the development of sarcoma. This occurred after serial transfers in heterogenous media and with addition of small amounts of methylcholanthrene, or perhaps even without such an addition. Earle considered therefore the possibility that fibroblasts may be able to undergo these changes by growing in tissue culture in heterogenous media without the action of cancerigenic hydrocarbons. Gey from similar experiments concluded that the action of methylcholanthrene is not required in order to obtain such a sarcomatous transformation. Do we have in these experiments to deal solely with the effect of long continued growth processes which take place under special conditions and which lead to the production of the autocatalytic growth substances in the fibroblasts, or is the addition of methylcholanthrene at least in part responsible for the results? Or are real viruses involved? Recent experiments of Sinai and Rifkind raise similar questions and they believe that they have obtained tumors after transplantation of apparently normal tissue under certain special conditions. The solution of these and various other problems must be left to future investigations and they may make more definite the line of demarcation between tumors in which true viruses are involved and those tumors which are caused by autocatalytically propagating, intracellular growth substances. However in giving due consideration to the experiments mentioned which need further investigation, there are a number of facts which make the view that extraneous viruses are the general immediate cause of cancer improbable. They are as follows: 1) In the majority of the mammalian and even of avian cancers it has been found impossible to demonstrate the presence of a virus. 2) The origin of such agents as those active in avian sarcoma and of the milk factor is unknown. 3) Effective cancer-producing agents such as hormones and certain polycyclic hydrocarbons and some other organic compounds are by themselves able gradually to push forward the growth activity of the tissue on which they act to such a point that the tissue becomes sensitized and at last becomes cancerous; even then the stimulation may not cease but by continuous action may intensify the cancerous state. It should again be emphasized in this connection that it is not sufficient for tissues to be for a short time in a state of active growth, in order

to become cancerous, but that a progressive concerted tissue growth, extending over a considerable period of time and caused and directed by the quantitatively coördinated action of extraneous stimulating and inherent genetic factors, must precede the development of cancer. 4) The stimulating substances seem to accomplish these effects not by transforming individual cells, as might be expected, if a virus acted on a tissue, or if a somatic mutation occurred, but it is a tissue unit as a whole which is thus affected and which in the end undergoes the cancerous change. 5) All those factors which inhibit or promote these growth processes influence in a corresponding way the development of cancer. Thus antagonistic hormone actions, general growth inhibitors, undernourishment tend to inhibit each in its own way the process of cancerization. 6) The more apt a tissue is to grow, the more readily it can be converted into cancer, a fact which applies also to embryonic tissues. This is borne out among others by the recent experiments of Greene and of Smith and Rous which indicate the great responsiveness of embryonic tissue to growth stimuli and its ready conversion into cancerous tissue, provided the genetic factors are suitable for such an effect. 7) Mention should also be made of one of the difficulties that might have to be faced if the milk factor were to be considered a true virus, whose function it is to transform the normal into cancerous mammary gland tissue. It would then be necessary to assume that the mammary gland tissues react to a virus of a different kind in those cases in which mammary cancer is induced without the coöperation of the milk agent and that this second virus would have to take over the function usually assigned to the milk factor. 8) The fact that Shope papilloma virus and milk factor act in the production of cancer not unlike certain chemical substances, which stimulate tissues to grow, or like hormones which induce proliferative processes, suggests that in other cases such chemical substances by themselves might be able to induce cancer formation.

We conclude then although in view of as yet existing uncertainties, only with certain reservations that the theory of autocatalytically active growth promoters which are derived from constituents of the tissue cells and originate in the course of the transformation of the normal cells into cancerous cells appears best to explain the development of the large majority of all cancers.

DISEASES OF THE COLLAGEN SYSTEM*

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THE term *collagen system* implies that the fiber-forming connective tissues which are distributed throughout the body represent an organic whole united by identity of basic texture as well as by similarity of function. Connective tissue is composed of cells and intercellular substance; the latter consists of fibers and a homogeneous ground substance. Upon boiling with water connective tissue yields a colloidal solution of animal glue or gelatin. For this reason the term collagenous tissue is used as a synonym for connective tissue. However, since collagen is derived entirely from the intercellular component of connective tissue, the designation collagen tissue places emphasis upon the intercellular substances. Thus the term collagen system points to the structural and chemical unity of these constituents of the connective tissue.

The term connective tissue connotes only the mechanical function of this bodily material. Yet other functions such as water and salt balance and the transference of metabolites from the blood to the parenchymal cells can also be attributed to it. The supportive functions evidently depend upon the tensile strength of the connective tissue fibers, while the colloidal nature of the ground substance makes it eminently suitable for the performance of metabolic functions. Again it is the extracellular portion of the connective tissue which presents a unity of action and thus justifies the term collagen system.

By providing a framework for the specialized parenchymatous cells, connective tissue plays an important role in the construction of all organs. In addition, in many organs it forms distinctive masses, such as the heart valves, which are structurally and functionally essential. Abnormal states of the connective tissue in such sites will obviously be reflected in morbid manifestations of the organs affected. Since our medical and especially our diagnostic notions have been expressed mainly

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in terms of organ pathology, morbid states of the collagen system have been interpreted as diseases of those organs which are most prominently implicated.

A review of the various concepts of disseminated lupus erythematosus and of generalized scleroderma will illustrate the gradual progress of our anatomic and pathologic comprehension of diseases of the collagen system; the history of rheumatic fever could serve equally well as an illustration. Both lupus erythematosus and scleroderma were originally regarded as diseases of the integument. The intense local and constitutional symptoms in disseminated lupus were recognized by Kaposi[1] as fundamentally different from those of localized lupus erythematosus. As early as the beginning of the present century Jadassohn[2] referred to disseminated lupus erythematosus as a constitutional disease. He stressed the occurrence of joint symptoms, mucosal alterations, glandular swelling, and especially renal complications. While these and subsequent clinical observations pointed to an involvement of internal organs, anatomical investigations disclosed no characteristic alterations other than those in the skin. Libman and Sacks[3] first called attention to conspicuous involvement of the endocardium; subsequently Gross[4] amplified these observations. Baehr, Schifrin and I[5] observed characteristic alterations of blood vessels, especially in the kidneys. These histologic findings were confirmed by the investigations of Jarcho,[6] Denzer and Blumenthal,[7] and Ginzler and Fox.[8] The latter authors added necrotic foci in lymph nodes to the anatomical picture of disseminated lupus erythematosus. Libman and Sacks,[3] and Gross[4] defined the clinical syndrome of disseminated lupus erythematosus anatomically as a characteristic form of endocarditis. Baehr, Schifrin and I[5] in attempting to unify the histologic alterations observed in the heart, blood vessels and serous membranes, considered a primary endothelial alteration as the basic lesion. Keil[9] expressed a similar point of view in his vascular concept of lupus erythematosus.

In 1941 further investigations[10] caused us to reinterpret our anatomic observations. In these studies our attention was attracted to a striking alteration of the collagen tissue of the pericardium and myocardium. This change consisted of fibrinoid transformation of the fibers and swelling of the ground substance.

Minute study of the endocardium, blood vessels, serous membranes, skin, dispersed connective tissues of the mediastinum, retroperitoneum

and of the joint capsules disclosed identical lesions. In the spleen the collagen fibers in the adventitia of the central arteries were concentrically thickened. In lymph nodes the necrosis already described by Ginzler and Fox was traced to an alteration of the reticulum fibers. The ubiquitous occurrence of striking collagen alteration and its almost unique expression in the renal glomeruli and splenic arterioles seemed to us characteristic enough to serve as anatomic definition. Consequently we submitted the thesis that alteration of the collagenous system is the basic anatomic manifestation of disseminated lupus erythematosus.

We were aware that acute rheumatic fever is also distinguished by systemic involvement of collagenous tissue but we believed that the association of the specific Aschoff nodule with fibrinoid collagen changes and the absence of the characteristic renal and splenic lesions were sufficient to separate anatomically these two diseases which seemed also to be different on clinical grounds. Due consideration was likewise given to the presence of fibrinoid collagen alteration in periarteritis nodosa. The association with striking eosinophilic leukocytic infiltration, the prominent localization in the vessel wall and the far less conspicuous collagen changes at other sites were regarded as a cogent reason against identification of the anatomic lesions in disseminated lupus erythematosus and periarteritis nodosa.

Early histologic investigation of generalized scleroderma disclosed the characteristic thickening and homogenization of the collagen tissue in the corium. Similar sclerosis was soon observed within the vessels of the skin and in internal organs. Subsequently it was observed that the alimentary tract, lungs and skeletal muscle may also participate in this sclerosing process which obviously exerted its preponderant effect in the connective tissue framework of the organs. In association with this progressive sclerotic transformation of the collagenous tissue, fibrinoid alterations were observed by several authors, Masugi and Yä,[11] Pollack,[12] which showed some similarity in extent and localization with those occurring in disseminated lupus erythematosus. Conversely, since sclerosing collagen alterations were observed in the spleen in lupus a parallelism in the anatomic manifestations of both diseases could be inferred. However, it seems that the clinical dissimilarity of the two maladies should discourage any attempt to declare them identical. Indeed, the histologic features merely point to the possibility that the fibrinoid and sclerosing changes are different phases of a disturbed chemico-physical

state of the collagen tissue which has not yet been adequately defined. But the morphologic evidence certainly permits the conclusion that generalized scleroderma should also be included among the diseases characterized anatomically by implication of the collagen system.

By the use of the term diseases of the collagen system we wanted merely to call attention to the basic alteration found on histologic examination in certain maladies such as lupus erythematosus and scleroderma. We did not wish to assert that these diseases were thereby defined in an adequate manner.

Pathology aims at a full disclosure of the nature and causes of disease. The aim is slowly approached by a rational analysis of all the morbid manifestations. Alteration of organ and tissue structure, although an essential phenomenon of disease, is not the disease itself. Anatomic pathology perceives structure only. It proceeds from observation and description to a comparison of the morbid with the normal and thus establishes the criteria of structural abnormality. By trying to account for the development of deviations in texture it becomes morphologic pathology. Goethe refers to morphology as the science concerned with formation and transformation of living organisms. It is the ultimate object of medical investigation to establish the causal relation between the impact of external forces upon the human body and the manifestation of disease. By correlating altered structure with associated changes in the internal or external environment pathology enters upon the search for the reason of disease. But a multitude of factors is disclosed by searching clinical and laboratory observation. To select the essential factors requires acute discrimination and careful experimentation. The present state of opinion regarding the cause of diseases of the collagenous system illustrates the intricacy of an inquiry into pathogenesis. Indefinite toxins as well as specific bacteria, such as the tubercle bacillus, have been alleged as the cause of disseminated lupus erythematosus; but these notions have generally been abandoned.

Allergy was originally suggested as the etiologic factor in lupus erythematosus because of clinical considerations. The hypothesis has found support (Fox,[13] Teilum[14]) since the characteristic alteration of fibrinoid degeneration of collagen tissue has been recognized in this disease. Similar changes observed in scleroderma have led Masugi[11] and other pathologists to assume that this disease likewise is of allergic origin. The hypothesis which regards fibrinoid degeneration as allergic tissue

reaction is derived from the experimental observations of Gerlach[15] and Klinge[16] and from the deduction of Gruber[17] that the vascular necrosis in periarteritis nodosa is evidence of hyperergic inflammation. Subsequent investigations of Klinge[18] and his associates and of Rössle[19] have culminated in the belief that any disease characterized by fibrinoid change is presumably of allergic origin.

In recent years Rich[20] has strongly supported this view. It cannot be denied that fibrinoid collagen alteration is a feature of local anaphylaxis as seen in the Arthus phenomenon. Clinical and experimental observations strongly support the belief that periarteritis nodosa is of allergic origin. At the present time the allergic hypothesis in rheumatic fever deserves more recognition than any of the other explanations, such as specific organisms or dietary deficiency. Yet we must not lose sight of the fact that collagen alterations identical with or hardly distinguishable from those seen in allergy can be produced experimentally by various factors. Thus Tsai Tung Wu[21] showed that simple squeezing of the skin results in fibrinoid degeneration; Schosnig[22] observed fibrinoid collagen change in various acute bacterial infections. Fibrinoid alterations of coronary vessels have been seen by Meessen[23] in orthostatic collapse in rabbits. In experimental hypertension conspicuous vascular lesions simulating periarteritis nodosa have been reported repeatedly by Friedman et al[24] Smith et al,[25] Selye and Pentz.[26] Moreover the alteration which is found in collagen fibers in the base of a chronic peptic ulcer or in the vicinity of acute pancreatic necrosis is strikingly similar to fibrinoid collagen changes. Since such changes can hardly be attributed to an allergic factor, the conclusion seems justified that fibrinoid collagen alteration must not be interpreted solely and invariably as an expression of allergic reaction. This point of view, presented by us in 1942,[27] has been recently re-emphasized by Baehr and Pollack in a discussion of the lesions of disseminated lupus erythematosus and scleroderma.

Morphologic investigations of tissue changes in disease must aim at full comprehension of the physical and chemical factors responsible for the abnormal microscopic appearances. This goal of anatomic pathology is still far from being attained. Fibrinoid collagen alteration in particular demands searching analysis. Even the structure of normal collagenous tissue is still very incompletely understood and investigations of its chemical and physical constitution must precede an inquiry into its ab-

normal states. Investigations of the connective tissue fibers with the aid of the electron microscope and of x-ray diffraction have brought forward important information regarding its molecular structure. The nature of the homogeneous ground substance, its relation to the fibroblasts and to the collagenous fibers still awaits elucidation. Fragmentary observations suggest that the ground substance is composed of complicated mucoproteins. The colloidal state of this matrix is known to be affected by enzymes such as hyaluronidase. Various female sex hormones are known to exert opposite influence (Sprunt[28]). By repeated injections of estrogen L. Loeb and his associates[29] produced hyaline changes in the stroma of various organs and H. Selye[30] provoked strikingly mucinous edema of the skin in hairless mice by the application of estradiol to the skin. The relation of ascorbic acid to the formation of fibers from the ground substance has been ascertained by Wolbach and Howe.[31] Bacterial enzymes have been discovered which act as collagenases. It is necessary to unite these fragmentary observations in a comprehensive rational system. By means of purposeful experimental studies in morphology we must try to identify the structural alteration of connective tissue in terms of reactions to well-defined chemical and physical influences. The term diseases of the collagen system merely refers to the fact that alterations of the extracellular portions of the connective tissue are prominent and systemic in various diseases. Such a designation would seem to lump together such heterogeneous maladies as disseminated lupus erythematosus, generalized scleroderma, rheumatic fever, and even periarteritis nodosa. This result would be regrettable. By calling attention to the collagen tissue as a common denominator, we only wanted to indicate that this tissue may be the common anatomic site of several diseases. But we have also stressed the dissimilarities, such as the characteristic granulomatous proliferation in rheumatic fever and periarteritis nodosa and the prominent sclerosing collagen alteration in scleroderma. In referring to fibrinoid changes of collagen as a phenomenon common to all these morbid entities we must not fail to emphasize that fibrinoid change can be provoked by a variety of factors. Consequently its occurrence in different diseases must not be interpreted as indicating that these diseases are identical or even related. Parenthetically it still seems necessary to inquire whether the apparent microscopic identity of fibrinoid collagen in such heterogeneous situations might not be a delusion. Investigations of the ultimate

structure of the collagenous tissue under controlled conditions must precede further inquiry into diseases characterized by lesions of this tissue. Only if we penetrate to the basic factors responsible for aberration of structure of the collagenous tissue shall we be able to define the diverse entities which constitute the group collectively termed diseases of the collagenous system.

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STREPTOMYCIN DOSAGE SCHEDULES FOR CLINICAL USE* **

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FOLLOWING the original publication on streptomycin by Schatz, Bugie and Waksman,[1] various exploratory clinical and laboratory investigations[2, 3, 4, 5, 6] were reported which demonstrated the effectiveness of streptomycin in treatment of certain microbic diseases. Additional significant contributions[7, 8, 9, 10, 11, 12] have appeared dealing with the pharmacology and toxicology of this antibiotic. In view of these encouraging reports, additional study of the factors involved in plannning a treatment program for clinical use of streptomycin seemed appropriate, the primary purpose being the formulation of simplified, rational dosage schedules. The presentation and analysis of pertinent data is the subject matter of this communication.

Oral administration of streptomycin is not feasible inasmuch as the drug is not absorbed consistently or in satisfactory concentration from the gastrointestinal tract. Inasmuch as intravenous administration of the presently available supply of streptomycin frequently induces pyrogenic reactions and other toxic manifestations the intramuscular route, apart from technical considerations, is the method of choice.

METHODS

Blood levels were determined periodically for 24 to 36 hours following a single intramuscular injection of streptomycin† in varying dosages. Concomitant assays were made of the urinary excretion of the antibiotic. The method for estimating streptomycin concentrations in body fluids[13] which was employed in this study, is a modification and adaptation of the technic developed for assaying penicillin.[14] The assay for streptomycin was made more sensitive and selective by adapting *Klebsi-*

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ella pneumoniae #41 as test organism. This organism is readily inhibited by streptomycin and is resistant to penicillin. The test under these circumstances has the added advantage of being applicable in those instances where streptomycin and penicillin are combined in the treatment program.

The procedure for performing the in vitro sensitivity test for streptomycin is as follows:

Test tube sensitivity to streptomycin is determined in essentially the same manner as penicillin sensitivity.[15] Bacteriostatic and minimal lethal dosage end points are estimated. The test medium is brain heart infusion broth (Difco) and the standard contains 800 micrograms per c.c. in water. Thirteen test tubes are prepared; 1.6 c.c. of broth is apportioned to the first tube, and 1 c.c. to the succeeding 12 tubes. Four-tenths c.c. of the streptomycin standard is added to the first tube and two-fold dilutions are made in the following 11 of the set up tubes. The last tube serves as control. This gives a reading range between 80-0.04 micrograms (Fig. 1). The organisms to be tested are grown in brain heart infusion broth for 18 hours and, depending upon the density of the culture, diluted 10^{-3}, or 10^{-4}. One c.c. of the diluted culture is inoculated into each of the 13 tubes. The tubes are then incubated overnight and read for bacteriostasis. All tubes with evidence of growth are discarded; the remaining tubes receive an additional 10 c.c. of broth and are reincubated for 24 hours. The test is then read for the minimal lethal dosage end point.

Results

A composite graph (Fig. 2) reveals the consistent presence of detectable amounts of streptomycin in the blood stream for 24-36 hours following a single intramuscular injection of 0.25, 0.5 and 1 gm. of the antibiotic in aqueous solution. Maximum levels were achieved within the first 12 hours followed by gradual tapering off to still assayable levels within the ensuing 12 hour period.

Figure 1—DILUTION SCALE

Tube No.	1	2	3	4	5	6	7	8	9	10	11	12	*Control*
Micrograms	80	40	20	10	5	2.5	1.25	0.63	0.32	0.16	0.08	0.04	0

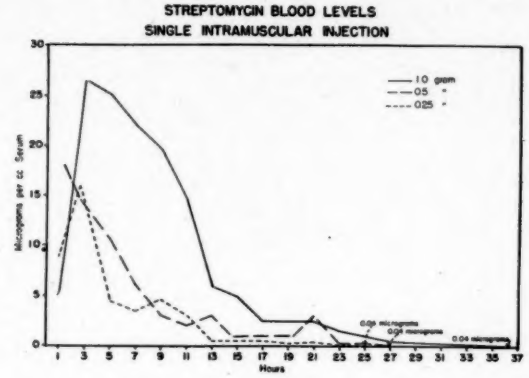

Fig. 2

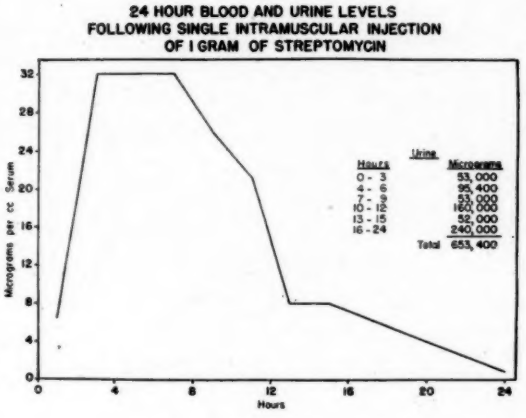

Fig. 3

At peak levels, the average streptomycin values ranged from 16 to 26 micrograms per c.c. of blood. The levels following the injection of 0.5 gm. reached a peak of 18 micrograms within one hour and then leveled off to 8.5, 6 and 4.5 micrograms at the sixth. seventh, and eighth hours, respectively. These concentrations are considered adequate for many of the streptomycin inhibitable organisms.

The curve of urinary excretion of streptomycin may parallel that of the blood concentration. A graph of values (Fig. 3) following a single intramuscular injection of 1 gm. of streptomycin portrays such parallelism and also indicates the retarded tempo with which the anti-

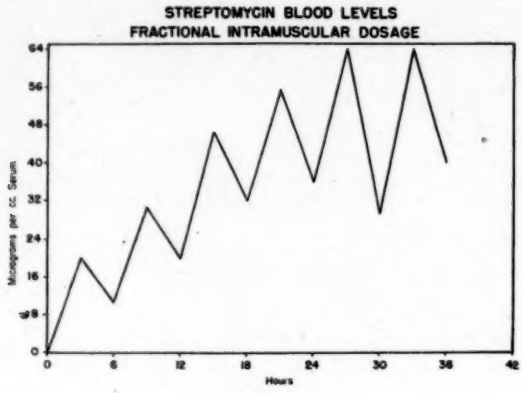

Fig. 4

biotic was eliminated. It is observed that, unlike penicillin where 60 per cent of a given dose may be recovered in the urine within one hour, in the case of streptomycin this was distributed over a period of 24 hours. A plateau type of excretion was apparent rather than an abrupt rise and fall.

In another series of studies blood levels were assayed periodically following repeated 6 hourly injections of 0.5 gm. of streptomycin. The graph of the levels (Fig. 4) clearly indicates additive, cumulative effects until a period of equilibration was achieved. The peak level of 64 micrograms per c.c. of blood is adequate for many of the microbic diseases amenable to streptomycin therapy. Ideally, the blood levels of antibiotics, particularly in the case of streptomycin. should far exceed the in vitro sensitivity value for the infecting organisms.

Discussion

The intermittent, intramuscular injection of aqueous solutions of antibiotics is irksome when repeated every 3 or 4 hours. This schedule is mandatory for penicillin because of the precipitate manner with which it is eliminated by the kidneys. Studies of penicillin excretion indicate that some 80 per cent of the antibiotic is lost through the renal tubular excretory apparatus, 60 per cent of a given single intramuscular dose being expended within the first hour of its administration.[16, 17, 18, 19, 20]

As a result of this phenomenon, methods have been developed for

retarding the absorption of penicillin and prolonging blood levels by means of intramuscular or subcutaneous repositories.[21, 22, 23] Other expedients, like sodium para-amino-hippurate, have been adopted for blocking the transport mechanism of the kidney thereby enhancing penicillin blood levels.[24, 25]

Pharmacological studies[7, 8, 9, 10] have shown that streptomycin looks primarily to glomerular filtration for its excretion. This makes for a much slower tempo of elimination through the kidneys with resulting augmentation and prolongation of streptomycin levels in the body fluids. The results of our own studies (Fig. 2, 3, 4) have confirmed the fact that streptomycin is excreted at a retarded rate as compared with penicillin. Peak levels were obtained for 6-8 hours and appreciable amounts were found in the urine for 24 hour periods following a single intramuscular injection of 0.25, 0.5 and 1.0 gm. of streptomycin.

Individual dosage is predicated on the in vitro streptomycin sensitivity tests of the infecting organism. It is important in antibiotic therapy. as previously reported,[15] to estimate both bacteriostatic and minimal lethal dosages according to the technique herein described. Studies in our laboratory have shown that dosage schedules dependent upon only the bacteriostatic activity of an antibiotic may be misleading especially when dealing with a protracted and refractory disease such as subacute bacterial endocarditis.[25, 26, 27, 28] In the course of our studies with antibiotic therapy, we realized the importance of determining the in vitro minimal lethal dose for the infecting organism in addition to the bacteriostatic end point and we accordingly modified our assays. Many treatment failures were thus avoided.

In correlating our investigative data in terms of the foregoing, it may be stated that for routine use with most of the streptomycin inhibitable organisms the dosage schedule of 0.5 gm. of streptomycin given intramuscularly every 6 hours will suffice. In point of fact, studies have indicated that adequate blood levels may be obtained for most of the treatment day when 0.5 gm. is given but twice daily. This dosage plan, however, is not recommended because of the well-known property of streptomycin to induce organism resistance or even fastness with subcurative doses. The dosage schedule should, of course, be intensified up to the limit of tolerance, a total of 10 gm. daily, if indicated by the in vitro sensitivity value of the infecting organism.

The tendency for some bacterial strains to develop resistance to

streptomycin despite presumably adequate dosages, militates against this antibiotic agent. Additional disadvantages are the untoward reactions observed with streptomycin therapy.[3, 6, 7, 11, 12] The most frequent and serious of these toxic manifestations are the labyrinthine disturbances characterized by nystagmus, vertigo and unsteadiness in gait which may develop within 2 or 3 days after inaugurating therapy. The longer the span of treatment, the more likely will these complications supervene.

In order to obviate organism refractoriness, forestall serious involvement of the central nervous system and prevent pyrogenic reactions the intramuscular administration of 0.5 gm. of streptomycin every 6 hours for a span of 7-14 days is recommended as a conventional treatment program. In those instances where a longer span of treatment (4-5 weeks) is required because of the nature of the infection, toxic complications may almost uniformly be anticipated. In these cases it is suggested that the treatment be interrupted every two weeks for a variable period of days depending on the response of the patient and the clinical manifestations. In any event, a total dosage of 2 gm. per day, fractionated every 6 hours, is a simple, effective and convenient method of administering streptomycin.

Conclusion

The intramuscular administration of streptomycin is the method of choice. Streptomycin is retained in the blood in effective therapeutic concentration for relatively long periods of time thereby permitting a more convenient spacing of the intramuscular injections. Studies are in progress with retarding menstruums to level off the peaks and achieve still more prolonged effects.*

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